Approved by the Regents
May 14, 2009

PROMOTION RECOMMENDATION
UNIVERSITY OF MICHIGAN
MEDICAL SCHOOL
DEPARTMENT OF NEUROLOGY

Benjamin M. Segal, M.D., associate professor of neurology, with tenure, Department of Neurology, Medical School, is recommended for promotion to professor of neurology, with tenure, Department of Neurology, Medical School.

Academic Degrees:

M.D.	1988	Brown University
B.S.	1984	Brown University

Professional Record:

2007-present	Associate Professor of Neurology, University of Michigan
2004-2007	Associate Professor of Neurology, University of Rochester
1999-2004	Assistant Professor of Neurology, University of Rochester
1993-1999	Research Associate, Laboratory of Immunology, National Institutes of Health
1993-1997	Clinical Instructor of Neurology, Georgetown University

Summary of Evaluation:

Teaching: Dr. Segal is currently training two graduate students, three postdoctoral research fellows, and an undergraduate student in his laboratory. Over the past academic year, three graduate students have performed rotations under Dr. Segal's supervision in his laboratory at the University of Michigan. Over the past ten years, he has been the mentor for five graduate students who have gone on to win postdoctoral fellowships at the La Jolla Institute, Trudeau Institute, Emory University, and Amgen, Inc. He has served on the dissertation committees for 13 additional graduate students in immunology, pathology and neuroscience. In the recent past, Dr. Segal gave lectures for a graduate level course in introductory immunology as well as for courses on the Neurobiology of Disease and Principles of Neuroimmunology. He has initiated a Neuroimmunology Lecture series at the University of Michigan in which extramural experts give a talk on multiple sclerosis related topics twice a month.

Since arriving at the University of Michigan, Dr. Segal has initiated a clinical fellowship program in Multiple Sclerosis (MS) intended to train neurologists who have finished their residency, in the diagnosis and treatment of patients with MS and related disorders as well as in clinical trial design and execution. Dr. Tiffany Braley, the first fellow in the program, has been awarded a Sylvia Lowry fellowship grant from the National Multiple Sclerosis Society to support her training under Dr. Segal's mentorship. In addition, Dr. Segal is currently the faculty mentor for a neurology resident with an interest in MS. He is an active participant in the neurology resident lecture series and he has started a clinical case conference series in MS for medical students, residents, fellows and faculty, that meets bimonthly. He has third-year medical

student teaching responsibility at the Veterans Affairs Medical Center (VAMC) where he runs an MS specialty clinic on a weekly basis. In addition, he attends formally on the neurology inpatient service two to four weeks per year and the neuroimmunology consultation service six months per year.

Dr. Segal has lectured extensively in the State of Michigan over the past year. During that time he has given several lectures to large patient audiences that were sponsored by the local chapter of the National Multiple Sclerosis Society. He has also given talks to community neurologists in Ann Arbor, Kalamazoo, Lansing and Grand Rapids and he has delivered grand rounds at the University of Michigan and Michigan State University.

In 2008, Dr. Segal gave platform presentations and chaired sessions at the American Association of Immunologists Annual Meeting (San Diego, CA) and the 9th International Congress of Neuroimmunology (Fort Worth, Texas). He was a plenary speaker at the Consortium of Multiple Sclerosis Centers (Washington, D.C.), the Lowentahl Conference of Neurological Disorders (Richmond, VA) and the annual meeting of the Veterans Affairs Multiple Sclerosis Centers of Excellence (Baltimore, MD). Between 2007 and 2008, he gave grand rounds at the University of Alabama, Harvard Medical School, UCLA, SUNY-Upstate, University of Pittsburgh, and the University of Rochester.

Research: Dr. Segal is an internationally respected scientist in neuroimmunology. He is particularly well known for his studies on cytokine and chemokine networks and leukocyte subsets in the pathogenesis of autoimmune demyelination. He oversees the Neuroimmunology Research Program at the University of Michigan. He is also the principal investigator of a Multiple Sclerosis Collaborative Research Center, sponsored by the National Multiple Sclerosis Society.

Dr. Segal is funded as principal investigator of grants from the NIH (R01, Autoimmunity Center of Excellence (ACE), special ACE award to study the mechanism of action of novel therapeutic agents in MS), the Dana Foundation and the National Multiple Sclerosis Society (research grant and MS Collaborative Research Center grant). Dr. Segal's team was one of the first two groups to demonstrate the importance of IL-12 monokines in the pathogenesis of experimental autoimmune demyelination (EAE), a widely used animal model for MS. Since then IL-12p40 monkines have been implicated in a wide spectrum of autoimmune diseases. His most recent publication on the topic shows that two distinct immune pathways, driven by distinct members of the IL-12p40 monokine family, can cause clinically indistinguishable forms of EAE (*J Exp Med.* 205(7):1535-41, 2008). However, each form of EAE responds differently to specific therapeutic interventions. By extrapolation, patients diagnosed with MS may fall into different categories, based on distinct underlying cellular and molecular pathways, that dictate whether they will respond favorably to a given therapeutic reagent. This work was recently featured in *Nature Reviews Immunology*. In addition, Dr. Segal was the principal investigator for a multicenter trial of a neutralizing antibody specific for IL-12p40 in relapsing remitting MS (*Lancet Neurol*ogy 7(9):796-804, 2008). The study was not positive. On-going studies are investigating whether this was secondary to poor penetration across the blood-brain-barrier or the presence of a redundant IL-12p40 independent pathway.

Dr. Segal is also well known for demonstrating a critical role of dendritic cells in EAE and MS. A recent study identifies the precursor cells that home to the CNS and differentiate into dendritic cells *in situ.* Future studies will identify the adhesion molecules and chemokines

necessary for dendritic cell accumulation in the CNS that might serve as future therapeutic targets.

Dr. Segal is a recipient of the Harry Weaver Neuroscience Faculty Award from the National Multiple Sclerosis Society and a Commendation Medal for Excellence in Research from the Public Health Service. He holds two patents for novel immunomodulatory therapies in multiple sclerosis (US Utility Patent Application No.s 11/119,333 and 60/64,323), one of which is currently optioned by a biotechnology company.

Recent and Significant Publications:

Carlson T, Kroenke M, Rao P, Lane TE, Segal BM: The Th17-ELR+ CXC chemokine pathway is essential for the development of CNS autoimmune disease. *J Exp Med.* 205(4): 811-823, 2008.

Kroenke MA, Carlson TJ, Andjelkovic A, Segal BM: IL-12 and IL-23 modulated T cells induce distinct types of EAE based on histology, CNS chemokine profile, and response to cytokine inhibition. *J Exp Med.* 205(7):1535-41, 2008.

Segal BM, Constantinescu CS, Raychaudhuri A, Kim L, Fidelus-Gort R, Kasper LH on behalf of the Ustekinumab MS Investigators: Phase II, double-blind, placebo-controlled, randomized, dose-ranging study of multiple subcutaneous injections of an anti-IL-12p40 neutralizing antibody, Ustekinumab, in patients with relapsing-remitting multiple sclerosis. *Lancet Neurol*ogy 7(9):796-804, 2008.

Deshpande P, King IL, and Segal BM: Cutting Edge: CNS $CD11c^+$ cells from mice with encephalomyelitis polarize Th17 cells and support $CD25^+CD4^+$ mediated immunosuppression, suggesting dual roles in the disease process. *Cutting Edge section, Journal of Immunology.* 178(11):6695-99, 2007.

Bagaeva LV, Rao P, Powers JM, Segal BM: CXC chemokine ligand 13 plays a role in experimental autoimmune encephalomyelitis. *Journal of Immunology* 176(12): 7676-85, 2006.

Service: Dr. Segal has provided excellent service to the University of Michigan since his arrival. He has initiated a bimonthly Neuroimmunology Lecture series that is open to all members of the academic community and that is highly popular. He has established a Multiple Sclerosis Collaborative Research Center that provides funding for collaborative projects related to MS to investigators throughout the medical school. He directs the Multiple Sclerosis Clinical Program and personally sees patients at the East Ann Arbor clinic half-day per week. In addition, he started an MS specialty clinic at the Veterans Administration Hospital that he attends another half-day per week. That clinic has since been named a Veterans Affairs Multiple Sclerosis Center of Excellence. He also attends on the Inpatient Neurology Service at the University of Michigan Hospital and at the VA Hospital for two to four weeks per year. He has started a Neuroimmunology Consultation service for the inpatient wards at the University of Michigan Hospital that provides evaluations and recommendations for patients admitted with MS or related disorders.

Dr. Segal has served as a permanent member of the Scientific Advisory Committee of the National Multiple Sclerosis Society since 2005 and as an ad hoc reviewer for seven NIH study sections over the past six years. He reviews abstracts for the American Neurological Association Annual Meeting/Neuroimmunology Block. He is also a member of the Clinical Advisory Committee for the local chapter of the National Multiple Sclerosis Society. His international standing is underscored by his work as an invited grant reviewer for many international organizations, including the United Kingdom's Wellcome Trust, the Multiple Sclerosis Society of Ireland, and the Multiple Sclerosis Society of Canada. He is an ad hoc reviewer for *Nature Immunology*, the *Journal of Experimental Medicine*, *Neurology*, the *Journal of Immunology*, the *Journal of Neuroimmunology* and *Brain, Behavior and Immunity*. At the University of Michigan, he serves on the Ad Hoc Planning Committee for the Future of the Department of Neurology and on the Instructional Track Promotions and Tenure Committee for the Department of Neurology. He is a member of the Programs in Immunology, Neuroscience and Biological Sciences.

External Review:

Reviewer A: "Dr. Segal is an outstanding neuroimmunologist whose recent work has transformed the way we view cell mediated autoimmune diseases....In my estimation, he ranks among the top 5% of the investigators in his field....Dr. Segal presents a combination of outstanding scholarly achievement, solid grant support, and a commitment to teaching, clinical care and service."

Reviewer B: "Dr. Segal is a superstar in my opinion. As an aside, I would love to have him join my department should he ever feel the need to move."

Reviewer C: "...Dr. Segal meets the criteria for promotion to full professor with tenure at the University of Michigan, and ranks in the top few percentile of his peers worldwide....In my opinion, he ranks in the top 5% of neuroimmunologists worldwide."

Reviewer D: "Ben Segal is an outstanding clinician-researcher, in every dimension....To make a bad pun (in a good cause), it is a 'no-brainer' to appoint Benjamin Segal as Professor of Neurology, and he would merit a comparable rank at [my institution]."

Reviewer E: "Since his arrival at Michigan, Dr. Segal has been able to assemble an outstanding group of scientists and clinicians and to establish a multiple sclerosis center as well as a neuroimmunology program....Dr. Segal has made important contributions to the field of neuroimmunology and multiple sclerosis therapeutics and will undoubtedly continue to do so."

Summary and Recommendation:

Dr. Segal is an internationally renowned physician-scientist who has already made tremendous contributions to the scholarship, service, and education at the University of Michigan. His past success and promise for the future make him a worthy candidate for promotion to professor, with tenure, in the Department of Neurology.

James O. Woolliscroft, M.D.
Dean
Lyle C. Roll Professor of Medicine

May 2009